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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,253	01/26/2005	Samual Weiss	16601-021US1	8661

26181 7590 02/05/2008

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EXAMINER	
MITCHELL, LAURA MCGILLEM	
ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
02/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/523,253	Applicant(s) WEISS, SAMUAL	
	Examiner Laura M. Mitchell	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 January 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1 and 3-18*.
   Claim(s) withdrawn from consideration: *19--40*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other:

Continuation Sheet

10. Applicants have presented a Declaration and arguments in the response filed 1/11/2008.

Claims 1, 3-4 and 10-18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of producing oligodendrocytes from multipotent neural stem cells isolated from mouse embryos and also an *in vivo* method to produce oligodendrocytes in mice comprising infusing mice with GM-CSF, does not reasonably provide enablement for a method of producing oligodendrocytes from all types of neural stem cells from any mammal at any developmental stage while the cells are located in a mammal other than a rodent (i.e. humans). **This rejection is being maintained for reasons of record in the previous Office Action, mailed 10/15/2007 and for reasons outlined below./**

The Applicant provided evidence in a Declaration under 37 C.F.R. § 1.132 filed 8/13/2007 ("First Weiss Declaration") that the claimed compounds are effective at producing oligodendrocytes in an animal model. Applicant submits that the data presented in the First Weiss Declaration demonstrated that administration of GM-CSF increases the production of new oligodendrocytes many fold in CD1 male mice. Further, the Applicant has provided data in Examples 1-4 of the specification showing the same effect *in vitro*. The Applicant provides herewith a second Declaration Under 37 C.F.R. § 1.132 by Samuel Weiss ("Second Weiss Declaration") stating that mouse animal models are accepted models for the evaluation of multipotent neural stem cells.

Applicant submits that the Federal Circuit has held that evidence showing that compounds within the scope of the claims that exhibit a recited activity *in vivo* "should [be] sufficient to satisfy the applicants' burden." In *re Brana,* 51 F. 3d 1560, 1567 (Fed. Cir. 1995). Applicant submits that while *In re Brana* specifically related to anti-tumor therapies and animal tumor models, one can reasonably extrapolate the findings to pertain to any novel therapeutic that is being tested in standard animal models of human disease. Therefore, Applicant submits that the demonstration by the Applicant that the recited oligodendrocyte promoting factors (OPF) promote the production of oligodendrocytes from multipotent neural stem cells both *in vitro and in vivo* in an accepted animal model is sufficient to establish the enablement of the present claims.

Applicant submits that in the cited cases, the Federal Circuit further addressed a contention that *"in vivo* tests in animals ... are not reasonably predictive of success in humans" by finding that this assertion confused "the requirements under law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *Id.* The Court found that "proof of an alleged pharmaceutical property of a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *Id.* (citing *In re Krimmel,* 292 F.2d 948 (CCPA 1961)). The Court indicated that "[w]e hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans." *Id.* at 1567 *(citing In re Krimmel,* 292 F.2d

948 (CCPA 1961). Applicant submits that the specification shows that the claimed molecules are pharmacologically active in an accepted animal model. Therefore, Applicant submits that the disclosure satisfies the enablement standard.

Applicant submits that the Office Action has set forth a much more rigorous standard, i.e., demonstrated efficacy in humans, than is required by the Federal Circuit. Applicant submits that the present application meets the standard set by the Federal Circuit of a demonstrated efficacy in a standard animal model. Applicant submits that more cannot be required by the Patent Office. In response to citation of Imitola et al in the rejection, Applicant submits that the Federal Circuit is willing to accept that a compound that exhibits a desirable pharmaceutical property in a standard experimental animal may not eventually have value in the treatment of humans. Applicant submits that a lack of human data does not preclude patentability and such data cannot be required by the Patent Office.

Applicant submits that the issue of undue experimentation has previously been addressed and dismissed by the Federal Circuit with regard to therapeutic compounds. Proof of human efficacy or FDA phase II testing is not required to meet § 112. *See In re Brana,* 51 F. 3d at 1568 *(citing Scott v. Finney,* 34 F. 3d 1058, 1063 (Fed. Cir. 1994)). "The stage at which an invention in this [pharmaceutical] field becomes useful is well before it is ready to be administered to humans." *Id.* at 1567. Requiring that a drug show efficacy in humans undermines the incentive to pursue patents in drugs in the first place because few companies if any could pursue the drug into phase II testing just to prove utility in humans, *Id.* "Usefulness in patent law, and in particular in the context of

pharmaceutical inventions necessarily includes the expectation of further research and development." *Id.* Applicant expects that human testing will be required to establish safety and efficacy prior to marketing the claimed compounds to produce oligodendrocytes from neural stem cells in humans; however, this form of research and development, *i.e.,* experimentation, is not considered undue or excessive by either the Federal Circuit or those skilled in the art. As set forth in the MPEP, "[t]here is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders, even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims." MPEP § 2107.03(c) III (Rev. 5, Aug. 2006) (citations omitted).

In the Declaration filed 1/11/2008, Dr. Weiss declares that mouse models are widely used by those of skill in the art to research properties of the human central nervous system (CNS) and treatment of CNS diseases. Dr. Weiss cites multiple recent scientific papers that use mouse models to research properties of the CNS and CNS diseases and conditions (see Second Weiss Declaration page 3-4). Dr. Weiss declares that he commonly uses mouse models in his research regarding neural stem cell properties. Dr. Weiss cites multiple scientific papers of his own work (see Second Weiss Declaration page 4-5). Dr Weiss declares that as demonstrated by the cited papers, mouse models for research into properties of the CNS, CNS diseases and treatments are widely accepted. These models provide valuable tools in the screening and development of novel drugs for the treatment of CNS diseases conditions. Dr.

Weiss declares that while mouse models may not be able to predict with 100% accuracy the efficacy of compounds for the treatment of stem cell related diseases and conditions in humans, the models provide valuable information that may lead to novel treatments of neurologic dishes and conditions in humans. Dr. Weiss declares that the present specification and earlier submitted declaration ("the First Weiss Declaration") provide *in vitro* and *in vivo* evidence that disclosed compounds promote oligodendrocyte production from neural stem cells. Specifically, the specification and the Weiss Declaration demonstrate that GM-CSF promotes oligodendrocyte production from neural stem ceils.

Response to Arguments

The Declaration under 37 CFR 1.132 filed 1/11/2008 is insufficient to overcome the rejection of claims 1, 3-4 and 10-18 based upon 35 U.S.C. 112, first paragraph (enablement) as set forth in the last Office action because: the claimed methods are not routine in the art. Given the breadth of the claims, state and unpredictability of the art with regard to the mammals in which the method will be practiced, the experimental data provided combined with the specification and the cited references showing mouse models does not provide sufficient description so that the skilled artisan could practice the method as claimed without excessive trial and error experimentation. The claimed methods are not routine in the art. Determination of a sufficient enabling disclosure is determined by a Wands analysis of the Forman factors and the other factors must be considered along with the working example of one aspect of the inventive method.

The claims are drawn to an *in vivo* method of differentiation of neural stem cells into oligodendrocytes using an OPF, which encompasses a very broad genus of any kind of mammal including humans with demyelinating disease. Although Applicant submits that the demonstration that the recited OPF promote the production of oligodendrocytes from multipotent neural stem cells both *in vitro and in vivo* in an accepted animal model is sufficient to establish the enablement of the present claims, the claimed method encompasses more than simple administration of an OPF as a therapeutic compound. The method as claimed encompasses contacting broadly claimed "multipotent neural stem cells" with an OPF *in vitro* and then administering the cells to the subject. Although Applicant has shown that OPF themselves are pharmacologically active in a rodent model, therapeutic transplant of stem cells is not considered routine in the art at present.

Applicants submit that the Office is requiring demonstrated efficacy in humans, as shown by citation of the Chandran reference, which discusses extrapolation of data from rodents to humans. However, citation of these references does not mean that the Office is not requiring more than is required by the Federal Circuit. The Chandran reference and the Imitola reference are cited in order to provide information regarding the state of the art of methods similar to the claimed method and to show that they are regarded by those skilled in the art as unpredictable. Human data or evidence of safety in humans is not required to meet the standard of enablement, however, the specification must provide a sufficient disclosure so that the skilled artisan would know

how to make and use the claimed method without undue and excessive experimentation.

The specification and Declaration do not provide specific guidance regarding dosages of any OPF to be administered to multipotent neural stem cells located in any mammal other than a mouse, including human mammals. The limitation of mammal encompasses mammals of any age and in any state of health. There is no guidance regarding whether there is any alteration in the method if the mammal is healthy, has been acutely injured or has had a demyelinating disease for many years. The specification does not provide sufficient guidance so that the skilled artisan would know how to use the claimed method to produce oligodendrocytes from multipotent neural stem cells without using excessive and undue trial and error experimentation. Given the state of the art, the unpredictability of the art, the lack of specific guidance and working examples, and scope and nature of the invention, the skilled artisan would have to practice excessive trial and error experimentation in order to be able to use the claimed method.

Claims 1 and 3-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is being maintained for reasons of record in the previous Office Action, mailed 10/15/2007 and for reasons outlined below**.

Applicant submits that they intends the standard English meaning of "derive" to be applied, i.e., to obtain or receive from a source. *Dictionary.com. The American Heritage Dictionary of the English Language, Fourth Edition. Houghton Mifflin Company,* 2004.http://dictionary.reference.com/browse/derived (accessed: January 9, 2008)). The American Heritage Dictionary also provides a definition for the word "derive" in a chemistry context, i.e., to produce or obtain (a compound) from another substance by chemical reaction, *Id. The* Office Action indicates, however, that the word "derived" has been interpreted as "derivative" and that the starting material is "derivatized." The Applicant does not believe that a substitution of the words "isolated" or "obtained" for is necessary because the word "derive" is defined as "to obtain or receive from a source" and the concept of a derivative is not suggested. Applicant submits that the choice of language and the Examiner's understanding actually correspond, and no change is required.

Applicant's arguments filed 1/11/2008 have been fully considered but they are not persuasive. Although Applicants have provided a definition of the word "derived", it does not provide sufficient metes and bounds of what Applicant intends. The claim does not provide any limiting characteristics of the multipotent neural stem cells or neural tissue from which they are derived. The term "neural tissue" is broad and does not comprise any identifying structural characteristics. The term "neural stem cell" is also broad and encompasses a large genus of cells in various stages of multipotency. Since the skilled artisan would not know how the multipotent neural stem cells are

derived from any type of "neural tissue", the metes and bounds of the claimed "multipotent neural stem cells" are not clear.

11. The request for consideration has been considered but does not place the applciation in condition for allowance because: Once a final rejection that is not premature has been entered in an application, applicant or patent owner no longer has any right to unrestricted further prosecution. Applicant is invited to review MPEP 714.12.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem Mitchell
Examiner
2/4/2008

CELINE QIAN, PH.D.
PRIMARY EXAMINER